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The Importance of Estrogen Replacement in Young Women with Turner Syndrome

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ABSTRACT

Background: **Most girls with Turner syndrome (TS) need estrogen replacement treatment (ERT) to induce and maintain feminization and prevent osteoporosis. There is abundant information on ERT use in postmenopausal women, but there is little information on this issue in women with TS. We aimed to determine the level of ERT use in women with TS living in the United States and assess the effects of ERT adherence vs. nonadherence on bone mineral density (BMD).**

Methods: **Fifty women with TS aged 30–59 years had ERT history obtained by structured interviews and BMD assessed at the lumbar spine by dual x-ray absorptiometry (DXA) and quantitative computed tomography (QCT).**

Results: **Thirty-four of the 50 women with TS had received ERT according to current recommendations, and the rest did not either because of physician failure to prescribe (5 of 50) or because of nonadherence to prescribed ERT (11 of 50). The mean duration of ERT was 25 ± 2 years for the standard of care group vs. 8 ± 2 years for the others ($p < 0.0001$). The major factor promoting adherence to ERT was education on the importance of ERT for bone health ($p < 0.001$). As expected, lumbar spine BMD was significantly reduced in women not taking ERT according to current guidelines (e.g., a reduction of 20% by QCT, $p < 0.001$) with 6 of 16 of these women having osteoporosis and 3 of 16 having vertebral compression fractures compared with 0 of 34 in the ERT adherent group.**

Conclusions: **Approximately 70% of women with TS in this sample of highly educated women in the United States are taking ERT as currently recommended and appear to be protected from osteoporosis of the spine, whereas those women using ERT less than 75% of the time are at grave risk for osteoporosis. In a time of new reservations about postmenopausal ERT, it is important to emphasize to young women with TS and their caregivers that ERT is critical for bone health.**

INTRODUCTION

TURNER SYNDROME (TS) RESULTS FROM complete or partial monosomy X and affects ~1 in 2000 live female births. The great majority of individuals with TS experience early ovarian failure, and thus estrogen replacement therapy (ERT) is required to induce and maintain feminization.[1] In addition, estrogen is clearly required for girls and young women to build and maintain good skeletal mineralization.[2] Although there have been studies on the rates of adherence with ERT in

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postmenopausal women[3,4] and in young women after surgical oophorectomy,[5] there is little information on the use of ERT in women with TS. It is not clear what percentage of medical practitioners are following the guidelines for estrogen treatment in TS, and it is also unknown what percentage of women with TS adhere to ERT when it is prescribed.

To illuminate these issues, we undertook this study in the context of an intramural National Institutes of Health (NIH) clinical protocol on genotype and phenotype in TS, which involved a 4–5-day stay in the NIH Clinical Research Center. Notably, this study was largely completed prior to the release of negative information about estrogen from the Women's Health Initiative (WHI) studies during this past year.[6,7]

MATERIALS AND METHODS

Study subjects

Study subjects were participating in an intramural, NICHD clinical study, Turner syndrome: Genotype and Phenotype. Recruitment for the study was largely through electronic media and publicity through the Turner Syndrome Society of the United States. Subjects were informed of the nature of the studies and signed informed consents that were approved by the NICHD IRB. Karyotype analysis of G-banded chromosomes in 50 peripheral blood cells was performed for all study subjects. Diagnosis of TS was based on karyotype showing complete or partial X-monosomy affecting $\geq 60\%$ of lymphocytes and the presence of typical clinical features, such as short stature and ovarian failure. The great majority of subjects were Caucasian (49 of 50), with 1 Asian participating in the study. Study subjects were euthyroid and in good general health as determined by clinical and laboratory evaluations on admission. Because the purpose of this study was to evaluate adherence with estrogen replacement and its effects on body mass index (BMD), we included only women ≥ 30 years.

Data on estrogen use and risk factors for osteoporosis

A survey about estrogen use over the life span was administered by a study investigator to each participant during the inpatient evaluation. Each subject was interviewed concerning the age ERT was started, discontinued, or interrupted over the life span. If subjects discontinued or interrupted ERT use, they were asked the reason for this. The subjects were also asked to recall the name brand and dosages of ERT taken. Index of adherence with ERT was calculated in the following way: years of actual ERT/(current age $-$ 15) if the subject had no spontaneous puberty, or years of actual ERT/(current age $-$ age of amenorrhea) if the subject had spontaneous puberty. All women who had an index of adherance ≥ 0.75 (75%) were considered to have received standard of care ERT. Additional information about educational level, tobacco and alcohol exposure, the use of medical services, and specific education about ERT's importance for bone health was also obtained from interview and routine health questionnaire and medical history. A psychologist used the Structured Clinical Interview for DSM-4 (axis I disorders) to determine if study subjects had any history of psychological disorders, including anorexia nervosa or bulimia, that might influence ERT adherence or BMD.

BMD

All women underwent measurement of areal BMD at the lumbar spine (posterior/anterior and lateral, L2–L4) using a Hologic QDR-4500A dual energy x-ray absorptiometer (DXA) (Hologic, Inc., Bedford, MA) with fan-beam technology. Z-scores were calculated based on manufacturer's age control data. To minimize the bias of DXA toward underestimation of BMD of small subjects and thus avoid overdiagnosis of osteoporosis, we corrected the measured areal BMD for body surface area as previously described[8] and then calculated T-scores using the corrected areal BMD and normative data from the manufacturer. All subjects also underwent quantitative, 3-dimensional CT of vertebral bodies L1–L2 (QCT). A GE Highspeed Advantage Scanner was used. Helical scanning from the inferior margin of T12 to the superior margin of L3 was performed to include a 3×3-mm intercorporal area of interest. Average volumetric BMD was derived for trabecular bone of L1 and L2 by image analysis performed by QCT PRO® system (Mindways Software, Inc., San Francisco, CA). A simultaneous solid CT calibration phantom, cross-calibrated against a University of California San Francisco (UCSF)-designed liquid K_2HPO_4 standard, was used. The

results were given in milligrams/milliliter of K_2HPO_4 equivalent. Z-scores were calculated based on software-incorporated data from UCSF normal controls. Manufacturer reported precision was 0.7%. Plain x-rays of the spine were taken to evaluate for the presence of skeletal abnormalities.

Statistics

Results are presented as means with standard error, medians with range, or percentages where appropriate. Group differences were evaluated by ANOVA followed by Fisher's protected least significant difference (PLSD). Where the distribution of data was not normal or the variance of data was not equal, rank-sum test was used. Comparison of proportions was by Z-test with Yates correction.

RESULTS

ERT use

The 50 women with TS who participated in this study were divided into groups based on the percentage of time they took ERT, beginning from age 15 if there was no spontaneous puberty or from the age of ovarian failure if it occurred later in life to the present (or to age 50 if >50 years of age). The adherent group included 34 women who had taken ERT for $\geq 75\%$ of this time. Of the remaining women, 5 either had a diagnosis very late in life or were advised against ERT by their physicians in the absence of any medical contraindication. Eleven women were prescribed ERT according to current recommendations but actually took it for $<75\%$ of the time (these latter two groups together are termed "nonadherent"). At the time of entry into the study, approximately 50% of the adherent women used oral contraceptives for ERT, about 25% used conjugated estrogens, and the rest used a mixture of oral and transdermal estradiol. All but 1 of the women taking estrogen also took either cyclic or continuous progestin formulations. There were no reports of venous thrombosis, embolism, stroke, breast cancer, exacerbation of hypertension, or diabetes among estrogen users in this study.

Table 1 compares adherent vs. nonadherent groups. The current age, the age when the diagnosis of TS was made, and the age when ERT was prescribed were similar in the two groups. As expected, the years of estrogen exposure were significantly less in the nonadherent group (Table 1). Although total years of formal education were not different, more women in the adherent group had received specific education from the healthcare provider concerning the benefits of ERT for bone health. Of the 11 women in the nonadherent group, 6 women did not want to have menses or had intolerable menstrual symptoms. The rest thought it was unimportant (4) or too costly (1) to take estrogen.

The majority of study subjects were cared for by family practitioners and gynecologists, with lesser numbers seeing internists or subspecialists (e.g., endocrinologists), and no pattern was apparent regarding ERT adherence and type of practitioner.

ERT and BMD

Inadequate ERT is expected to cause impaired bone mineralization during the adolescent years

Table 1. ERT in Turner Syndrome[a]

Characteristic	*Adherent* (n = *34*)	*Nonadherent* (n = *11*)	p *value*
Age (years)	41 ± 1.4	41 ± 2.0	0.94
Age at diagnosis (years)	13 ± 1.4	12 ± 2.8	0.8
Age started ERT (years)	16 ± 0.8	18 ± 1.4	0.2
Years ERT taken	25 ± 1.5	10 ± 1.9	<0.0001
Years of education	16 (12–20)	16 (12–18)	0.07[b]
ERT education received, *n* (%)	28/34 (82)	3/11 (27)	0.0003

[a]The adherent group were diagnosed with TS, were prescribed ERT in a timely manner, and used ERT for ≥75% of the time since first prescribed. The nonadherent group had the same medical care but took ERT as prescribed for <75% of the time.

[b]Rank-sum test.

and contribute to loss of bone mineral in adults. Therefore, we compared BMD at the lumbar spine in the two groups using areal DXA and volumetric QCT. In this analysis, we included all women who did not receive standard ERT irrespective of the cause (nonadherent; $n = 16$). As shown in Table 2, lumbar spine BMD was significantly reduced in this group by every measure. Notably, the BMD obtained by QCT, which is independent of a person's size, showed a 20% reduction in inadequately treated women compared with standard of care women. Six of the 16 women in this group vs. none of the 34 women in the standard of care group had osteoporosis (T-score ≤ -2.5, $p = 0.0001$). There were 3 cases of vertebral compression fracture in the nonadherent group and none among the adherent. The reduction in BMD was most severe in the women who had taken ERT for the least time because of a very delayed diagnosis or failure of the physician to recommend ERT (data not shown). Interestingly, a history of an eating disorder (anorexia or bulimia) was more prevalent in the standard of care group. There was very little tobacco or alcohol use among women with TS participating in this study. None consumed more than 3–4 drinks/week, and there was only 1 smoker, who used 3–4 cigarettes a day (in the adherent group).

A dramatic illustration of the importance of ERT in young women with TS is shown in Figure 1, in which plain spine x-rays show deformation and compression fractures of thoracic vertebral bodies of a young woman who took ERT $< 50\%$ of the time.

DISCUSSION

We found that only 68% of adult women with TS in the United States, as sampled in this study, are taking ERT according to current guidelines.[1] Among women who were diagnosed in a timely manner and prescribed ERT (45 of 50, 90%), the major factor predictive of ERT adherence was the exposure to education about the importance of ERT for maintaining bone health. Eleven of these women receiving appropriate care (~25%) discontinued ERT because of discomfort with menstrual cycling and a lack of appreciation of the value of ERT for bone health. Adherence among this group might be improved with more attention to individualized ERT regimens and reinforcement as to ERT's importance for bone health. Five of the 50 women studied had received suboptimal medical treatment, either because the diagnosis TS was delayed until it was too late to prevent osteoporosis or because their physicians did not recognize the importance of ERT in young women with TS. It should be noted that these women were among the oldest study participants, and knowledge about TS and the importance of ERT was not widespread during their youth.

Our study observations probably reflect an optimistic view of ERT use among women with TS throughout the United States. Most of our study subjects learned about the study on the worldwide web and through interaction with the Turner Syndrome Society, USA (*www.turner-syndrome-us.org*) or through word-of-mouth from study participants. Participation in the NIH study

Table 2. ERT and Lumbar Spine BMD in Turner Syndrome

Characteristic	*ERT ≥75%* (n = *34*)	*ERT <75%* (n = *16*)	p *value*
Age (years)	42 ± 1.4	42 ± 2.1	0.8
Height (cm)	144.2 ± 1.1	145.2 ± 1.9	0.6
Weight (kg)	54 (36–150)	61 (40–120)	0.23[a]
BMI (kg/m^2)	25 (18–47)	29 (20–54)	0.04[a]
Years ERT taken	25 ± 1.5	8 ± 1.6	<0.0001
Eating disorders, *n* (%)	5/34 (15)	1/16 (6)	0.37
DXA LS-AP BMD (g/cm^2)	0.91 ± 0.02	0.75 ± 0.03	<0.0001
DXA LS-AP Z-score	−0.9 ± 0.2	−1.9 ± 0.3	0.002
QCT LS BMD (mg/cm^3)	137 ± 3.8	109 ± 6.8	0.0005
QCT LS Z-score	−0.6 ± 0.2	−2 ± 0.3	0.0001
Diagnosis of osteoporosis, *n* (%)[b]	0/34 (0)	6/16 (38)	0.0004

[a]Rank-sum test.

[b]The diagnosis of osteoporosis according to WHO criteria (T-score ≤ -2.5 SDs) is based on DXA data. DXA, however, is an areal method that tends to underestimate BMD in small people. Therefore, we corrected the measured areal BMD values for body surface area as previously described[8] and then calculated T-scores using the corrected areal BMD and normative data from the manufacturer.

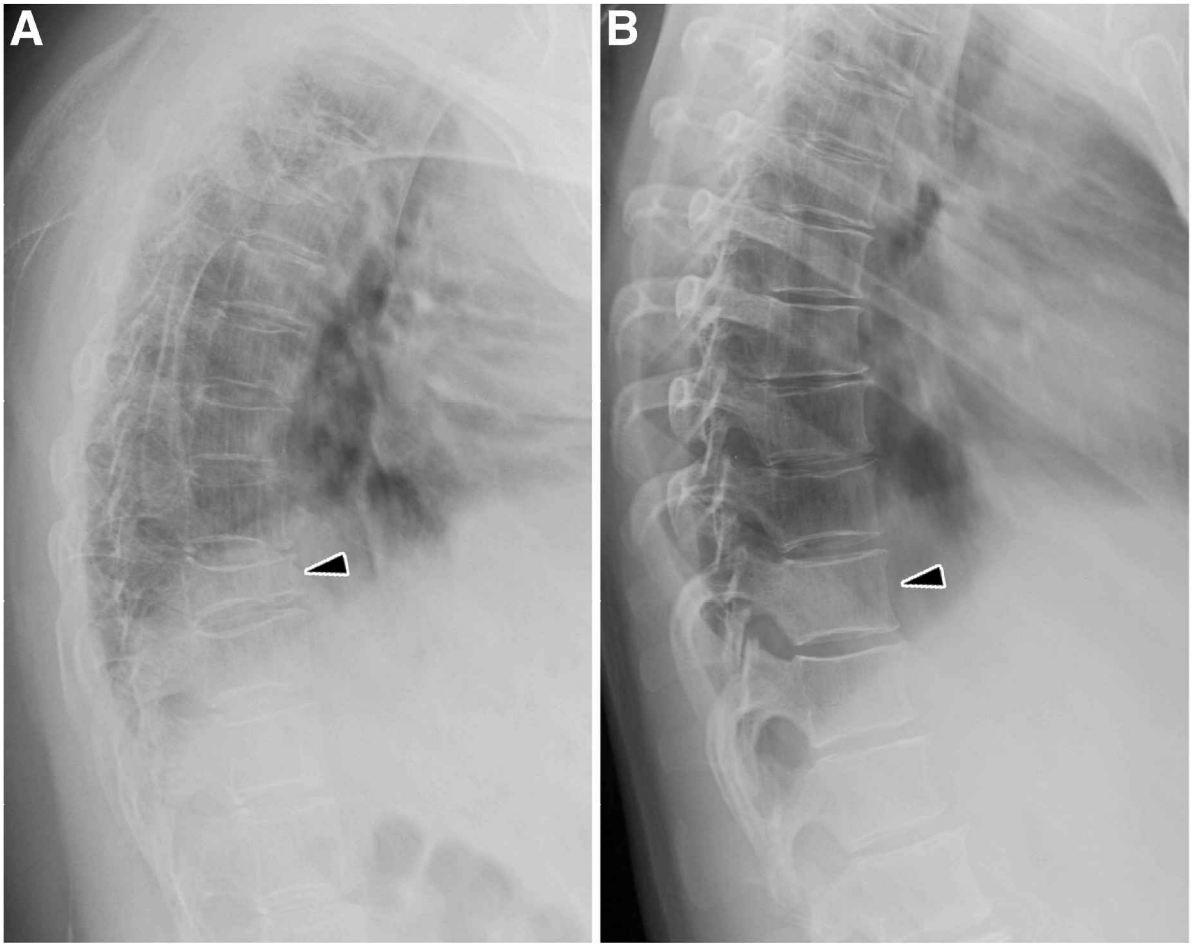

FIG. 1. (**A** and **B**) Lumbar spine x-rays show the effects of ERT nonadherence on vertebral strength. The vertebral bodies of the 33-year-old woman (**A**) are deformed and compressed (especially T9, arrow), causing chronic pain, kyphosis, and decreased height.

involves travel to Maryland for an inpatient evaluation lasting 4–5 days. Women who are not involved with electronic communications or TS societies or who are chronically ill or homebound for other reasons are likely underrepresented in this study group. The participants in our study had a higher degree of education (most having graduated from college) than the general population. Thus, the level of medical care and adherence to ERT in this group may represent the best end of the spectrum, and less educated or less proactive women with TS across the United States may not be doing so well.

There are more abundant data on treatment patterns for women with TS from Europe,[8–12] where national healthcare systems and registries make the standard of care more uniform and monitoring of treatment easier. One recent study from Denmark interviewed 60 women with TS, recruited through the Danish TS Society, and found that only 5 women had not taken ERT as recommended,[8] for an overall adherence rate of 92%, substantially higher than we found. That study reported that there was no difference in BMD at any site in women on ERT vs. those who never took ERT.[8] Details are not provided, so perhaps the women who declined ERT had very recent ovarian failure or were still young and, thus, did not yet exhibit any effects of hypogonadism on bone. Also, if the rate of clinical osteoporosis among untreated women is about 40%, as this study suggests, with only 5 untreated women, we expect only 2 cases, not enough to impact regression analyses among 60 study subjects.

This study clearly shows that ERT has important effects in maintaining BMD at the lumbar

spine in women with TS. Despite the important salutary effects of ERT on bone in TS, in the wake of the recent controversy concerning ERT risk in postmenopausal woman,[6,7,13] many patients with TS and their families are now questioning ERT safety and utility. In addition, some are pursuing alternative medicine or herbal supplements rather than standard ERT. Thus, it is important at this time to reinforce the importance of physiological estrogen replacement in young women with ovarian failure. This study has revealed that specific education from the healthcare provider about the importance of ERT for bone health was critical for ERT adherence, and we think that this is even more important now in a time of uncertainty about ERT risks and benefits.

In addressing the risk/benefit ratio of ERT for young women with TS or other causes of early ovarian failure, we note that the risk of breast cancer in normal premenopausal women is quite low, estimated at 0.03% over 5 years for women ≤ 35 and 0.08% per 5 years from age 35 to 50 (*seer.cancer.gov/faststats/html/inc_breast.html*). Although pharmacological ERT obviously does not perfectly replicate normal ovarian function and, thus, may theoretically increase breast cancer risk above that associated with normal ovarian function in young women, abundant data on breast cancer risk in young women taking oral contraceptives suggest that any increase in risk from ERT in this age group is very small.[14] In contrast, the risk of osteoporosis due to untreated ovarian failure in young women is great. In this study alone, almost 40% of inadequately treated women had osteoporosis diagnosed by DXA and ~20% had compression fractures. Although short-term adverse effects of ERT, such as blood clots and hypertriglyceridemia, have not been reported in women with TS, we advise patients of these possibilities and generally advocate the transdermal route for estradiol with cyclic progesterone as the most physiological regimen for long-term ERT in young women. It was recommended previously to continue ERT at 2 mg estradiol or equivalent daily until the usual age of menopause. In light of recent developments, however, we think it reasonable to reduce the dose to 1 mg after full feminization is attained. This view is based on a generally cautious approach and our observation that BMD appears to be well preserved in women on the lower dose, which is consistent with results from the PEPI trial showing maintanence of BMD in postmenopausal women taking 0.625 mg conjugated estrogens.[15]

In addition, we strongly advise weightbearing exercise along with adequate calcium and vitamin D intake for all women with TS to help build and maintain bone health. Although there is very extensive information on the risks and benefits of ERT, there is very little information on the long-term use of alternatives to prevent osteoporosis, such as bisposphonates, which also lack the desirable feminizing effects of estrogen. Thus, we continue to recommend ERT for young women with TS and other causes of premature ovarian failure. However, we suggest tapering and eventually discontinuing ERT for most women with TS approaching age 50, depending on individual circumstances and taking stock of all important health issues at that point, as one would do for any woman of that transitional age.

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